PTO/SB/17 (10-03)
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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003, Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 330.00

Complete if Known	
Application Number	09/436076
Filing Date	November 8, 1999
First Named Inventor	Robert C. Johnson
Examiner Name	G. R. Ewoldt
Art Unit	1644
Attorney Docket No.	CFBF-P03-002

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

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Deposit Account Name: Ropes & Gray LLP

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims		-** =		x		=	
Independent Claims		-** =		x		=	
Multiple Dependent						=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	330.00
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) ______

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 330.00

SUBMITTED BY

(Complete *(if applicable)*)

Name (Print/Type)	William G. Gosz	*Registration No. (Attorney/Agent)*	27,787	*Telephone*	(617) 951-7617
Signature	William G. Gosz			*Date*	April 14, 2004

TRANSMITTAL OF APPEAL BRIEF

Docket No.
CFBF-P03-002

In re Application of: Johnson et al.

Application No.	Filing Date	Examiner	Group Art Unit
09/436076	November 8, 1999	G. R. Ewoldt	1644

Invention: METHODS FOR TREATING AND PREVENTING ATHEROSCLEROSIS WITH CHIMERIC MOLECULES

TO THE COMMISSIONER OF PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed: December 1, 2003 .

The fee for filing this Appeal Brief is 330.00 .

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This sheet is submitted in duplicate.

William G. Gosz

Dated: April 14, 2004

William G. Gosz
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Attorney Docket No. CFBF-P03-002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant(s):	Wagner et al.	Examiner:	P. Gambel
Serial No.:	09/436,076	Art Unit:	1644
Filing Date:	November 8, 1999		
For:	METHOD FOR TREATING AND PREVENTING ATHEROSCLEROSIS		

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

The undersigned hereby certifies that this document is being placed in the United States mail with first-class postage attached, addressed to the Commissioner for Patents, Mail Stop Appeals, on 4/14/04.

Patricia McKenney

Mail Stop Appeal
Commissioner for Patents
P.O. 1450
Alexandria, VA. 22313-1450
ATTENTION: Board of Patent Appeals and Interferences

Sir:

APPELLANT'S BRIEF ON APPEAL

This is an appeal to the Board of Patent Appeals and Interferences (the "Board") from the decision of the Examiner finally rejecting claims 40, 41, 49-52, 59, 60 and 73, and is in furtherance of the Notice of Appeal filed on December 4, 2003, in this application. The appealed claims are as set forth in the attached Appendix. Provision for the payment of fees required for filing this brief, and any required extension of time for filing the brief, is submitted herewith. This brief is submitted in triplicate in accordance with the provisions of 37 C.F.R. §1.192(a).

REAL PARTY IN INTEREST

The real party in interest in this appeal is the CBR Institute for Biomedical Research, Inc., aka The Center for Blood Research, Inc., the assignee of the rights of the inventors in the above-identified patent application. The CBR Institute for Biomedical Research, Inc., is an affiliate of the Harvard Medical School.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences that will directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

STATUS OF CLAIMS

The status of the claims in this application is as follows. Claims 40, 41, 49-52, 59, 60 and 73 are pending and are on appeal. No claims have been allowed.

STATUS OF AMENDMENTS

Claims 40, 41, 49-52, 59, 60, 73 and 74 were finally rejected in the final Office Action of June 6, 2003. An Amendment After Final Rejection was filed on December 1, 2003. An advisory action was mailed to appellants on March, 12, 2004, and resulted in entry of the Amendment After Final Rejection for purposes of this appeal. The Amendment After Final Rejection amended claims 40, 51 and 73, and canceled claim 74. The claim amendments are reflected in the appended claims.

SUMMARY OF INVENTION

Atherosclerosis, a principal cause of heart attacks among adults in the United States, results from the restricted flow of arterial blood due to the accumulation of fibrous plaque over time in the arterial lumen. Death or incapacitation of the subject may result from the rupture of the fibrous cap of the plaque, causing hemorrhage, thrombosis and occlusion of the artery. The fibrous plaque is formed from fatty streaks which develop into lesions composed predominantly of layers of smooth muscle cells, lipid-filled macrophages and T cells. The earliest stages of atherosclerosis occur when migrating monocytes and T lymphocytes bind to the lumen of the arterial wall. Atherosclerosis is a chronic, ling term condition, as distinguished from more acute conditions such as local inflammation. Page 1, line 17 to page 2, line 22. Appellants have found that P-selectin is implicated in the origins of atherosclerosis as a result of the mediation of platelet or endothelial cell binding and adhesion to monocytes. Page 5.

In one embodiment, the claimed invention relates to a method for decreasing the formation or growth of atherosclerotic lesions, and for treating or inhibiting atherosclerosis in a mammal by the administration of an effective amount of a soluble chimeric molecule to the mammal. The chimeric molecule comprises P-selectin glycoprotein ligand-1, or a fragment thereof, and another molecule. The chimeric molecule is capable of inhibiting the interaction between P-selectin and a ligand of P-selectin, and is administered to the patient prior to, or in conjunction with, a vessel-corrective technique. Specific vessel-corrective techniques and administrative protocols are disclosed in the application. Page 4, lines 12-18, and page 8, line 28 to page 9, line 8.

In another embodiment, the claimed invention is directed to methods for treating restenosis in a mammal by performing a vessel corrective technique on the mammal, and subsequently administering an effective amount of a soluble chimeric construct, as defined above, to the mammal to treat restenosis occurring after a vessel-corrective technique. In this particular embodiment, the vessel-corrective technique is angioplasty, stenting procedure, atherectomy, and bypass surgery. Page 14, line 20-30.

ISSUES

The sole issue to be decided in this appeal is as follows:

Whether claims 40, 41, 49-52, 59, 60 and 73 are unpatentable under 35 U.S.C. 103(a) as obvious over Cummings et al. (U.S. Patent No. 6,309,639) in view of Tedder et al. (U.S. Patent No. 5,834,425) and Coller et al. (U.S. Patent No. 5,976,532).

GROUPING OF CLAIMS

Claims 40, 51 and 73 are independent claims. Claims 41, 49 and 50 are dependent on claim 40. Claims 52, 54 and 60 are dependent on claim 51. No claims are dependent on claim 73. Claim 40 is directed to methods for controlling the growth of atherosclerotic lesions. To the extent that claim 51 is interpreted as treating the development of atherosclerosis, as appellants urge, then claims 40 and 51 stand and fall together. Claim 73 is directed to methods for treating restenosis, and stands or falls on its own.

ARGUMENT

I. Rejection of Claims 40, 41, 49-52, 59, 60 and 73

Claims 40, 41, 49-52, 59, 60 and 73 have been rejected under 35 U.S.C. 103(a) as obvious over Cummings et al. (U.S. Patent No. 6,309,639) in view of Tedder et al. (U.S. Patent No. 5,834,425) and Coller et al. (U.S. Patent No. 5,976,532). Appellants respectfully request reversal of this rejection by the Board.

Appellants maintain that, as to the Cummings et al. reference, the Wagner declaration filed under 37 C.F.R. § 1.131 is adequate and sufficient to establish that the present invention was conceived prior to the effective date of the reference, and diligently reduced to practice thereafter. Consequently, it is appellants' position that the Cummings et al. primary reference has been effectively antedated, and is therefore not prior art. Alternatively, and notwithstanding the Wagner declaration, appellants also maintain that Cummings et al., either alone or in

combination with Tedder et al. and Coller et al., would not supply the necessary motivation to lead one skilled in the art to the present invention.

The Examiner has attacked the sufficiency of the Wagner declaration based on the following alleged shortcomings. The declaration states that the development of the knockout mouse model used in the reduction to practice occurred during the time period from November 16, 1992 to September 13, 1993, although appellants' experimental results were collected and analyzed on or about May 6, 1994. This represents a time period of some eight (8) months which is presumably viewed as excessive. Moreover, the declaration utilizes a knockout mouse model to simulate a deficiency of P-selectin, rather than a specific inhibitor of P-selectin and ligand binding, such as P-selectin glycoprotein ligand, or a chimeric construct including P-selectin glycoprotein ligand.

With regard to the question of diligence regarding the reduction to practice of the invention, the Wagner declaration (paragraphs 7 and 8) states that it took 8 months following the preparation of the mice for the mice to develop atherosclerosis due to the fact that the mice are resistant to atherosclerosis. The fact that it took 8 months for the mice to develop atherosclerosis is not unreasonable or unusual in light of this natural resistance to the formation of atherosclerosis plaque. Overcoming this resistance is a time consuming undertaking, involving feeding the mice a high lipid diet for a prolonged period of time. Since atherosclerosis is a long term, chronic condition, it is not unusual that it look the mice 8 months to develop symptoms of the disease. Note that the mice were fed a high lipid diet promptly after their genetic makeup was confirmed, and the mice were then sacrificed immediately thereafter. Thus, the work described in the Wagner declaration was undertaken diligently and expeditiously, even though the science necessarily imposes constraints on the speed with which the work could have been completed due to the inherent limitations of the mouse model as described.

The Examiner has also criticized the Wagner declaration as not being commensurate in scope with the scope of the appealed claims. In particular, the Examiner states that since the Wagner declaration fails to disclose a vessel corrective technique, or a method for treating restenosis, it is not commensurate with the scope of the claims. In this regard, the Examiner has taken the position that the Wagner declaration must establish possession of either the whole

invention as claimed, or a subset of the invention falling within the scope of the claims, citing *In re Tanczyn,* 146 USPQ 298 (CCPA 1976), and MPEP 715.02. Appellants respectfully disagree with this conclusion as applied to the facts of this appeal.

Appellants' position is that it is only necessary for the declaration to disclose all of the essential features of the reference being antedated. In this regard, see MPEP 515.02 which provides, in part, that where the differences between the claimed invention and the disclosure in the reference renders the claimed invention obvious, the declaration antedating the reference is required to show no more than what the reference shows. See also *In re Stryker*, 435 F.2d 1340, 168 USPQ 372 (CCPA 1971).

The Examiner has relied upon the Cummings et al. reference as disclosing the use of P-selectin glycoprotein ligand for the treatment of atherosclerosis. Although appellants disagree with the Examiner's characterization of Cummings et al., for purposes of the sufficiency of the Wagner et al. declaration, appellants assume this characterization of the reference is accurate. Appellants believe that a fair reading of the Wagner declaration demonstrates the conception of the invention as claimed by appellants and as described in the reference prior to 1988, the effective date of the reference, followed by a diligent reduction to practice thereafter.

The Wagner declaration utilizes a knockout mouse model deficient in P-selectin to establish the principal that a reduction in P-selectin level correlates with a reduction in the accumulation of atherosclerotic lesions and plaque, and a commensurate reduction in atherosclerosis. The use of the knockout mouse model is intended by the inventors to simulate the activity of an inhibitor of P-selectin and ligand binding, and is so stated in the declaration. Appellants submit that one skilled in this art would recognize that this is a standard approach to simulating the activity of an inhibitor over a long period of time, and would be recognized as such. The Board will appreciate the practical difficulties in the science involved in the invention, and that a method for preventing atherosclerosis, a long term, chronic condition, would be inherently difficult to reduce to practice. However, these difficulties should not preclude appellants from obtaining the fruits of their labor. It is noted, for instance, that the broad scope of the invention as originally claimed was not limited to particular inhibitors, and that the more limited claim scope now before the Board is the result of a restriction requirement imposed by

the Examiner. Notwithstanding, the showing made in the declaration is generic to both the invention now claimed and the reference, and is adequate to antedate the reference.

Appellants further dispute the Examiner's contention that Cummings et al. discloses the use of P-selectin glycoprotein ligand to prevent atherosclerosis. Cummings et al. discloses methods for inhibiting an inflammatory response and for inhibiting leukocyte adhesion using compounds that interfere with the binding of P-selectin. Among the compounds listed in the reference are P-selectin ligand, including the glycoprotein ligand, as well as antibodies to the ligand. Among the disorders listed in the reference are reperfusion injuries, ischemia, sepsis, adult respiratory syndrome, cancer, atherosclerosis and rheumatoid arthritis. See cols. 18 and 19 of the reference.

With respect to atherosclerosis, Cummings et al. states that the rupture of atherosclerotic plaque may lead to thrombus formation and ischemia. See col. 19, lines 57-64. Thus, Cummings et al. does not purport to use P-selectin ligands or antibodies to treat the origins or earliest stages of atherosclerosis. Rather, Cummings et al. treat the inflammatory condition resulting from the rupture of atherosclerotic lesions or plaque occurring which after the disease (atherosclerosis) has progressed to its end stages. This is distinct from the invention recited in appended claims 40, 41, 49 and 50, which are directed to preventing the formation or growth of atherosclerotic lesions, i.e. conditions leading to the development of atherosclerosis.

Significantly, Cummings et al. is silent on the use of vessel-corrective techniques, or the treatment of restenosis as a medical disorder. The Cummings et al. reference discloses that P-selectin glycoprotein ligand-1 inhibitors can function to reduce leukocyte adherence and inflammation. However, the reference fails to disclose that P-selectin glycoprotein ligand-1 inhibitors can be used in conjunction with surgical procedures.

Appellants reiterate that the claims on appeal are directed to methods for treating atherosclerosis, methods for reducing atherosclerotic lesions, and methods for treating restenosis. All of these claimed methods involve the use of surgical procedures. With regard to restenosis and atherosclerosis, appellants also reiterate that these conditions are art recognized as different medical disorders: restenosis refers to a renarrowing or blockage of an artery at the site where a surgical procedure, such as angioplasty or a stent procedure, has already occurred; whereas

atherosclerosis is a chronic, long term narrowing of blood vessels due to an accumulation of plaque in the arteries.

The Examiner has cited the Tedder at al. and Coller et al. secondary references in order to remedy the shortcomings of the Cummings et al. primary reference. Tedder et al. describes chimeric peptides or polypeptides that combine the ligand binding features of the domains of two different selectin molecules. The chimeric molecules of Tedder et al. are used to mediate leukocyte adhesion and function in the circulatory system, and are described as being useful as anti-inflammatory compounds, rather than for treating atherosclerosis or restenosis. There is no disclosure in Tedder et al. that these chimeric molecules can be used to treat atherosclerosis or restenosis, or that these molecules can be used to reduce lesions or plaque.

Tedder at al. has apparently been cited to show that chimeric P-selectin polypeptides are known in the art. However, appellants submit that the properties of these polypeptides as described in Tedder et al. would not lead one skilled in the art to conclude that such chimeric constructs can be used to treat atherosclerosis or restenosis.

Coller et al. is directed to methods for treating a thrombotic condition in a patient by the administration of a chimeric immunoglobulin directed to the glycoprotein IIb/IIIa receptor. Coller et al. states that the antibodies can be used in a variety of therapies involving thrombus formation, such as embolisms, ischemic attacks, deep vein thrombosis and coronary bypass surgery. The Examiner has contended that since Coller et al. teaches the use of thrombolytic agents to prevent platelet aggregation and thrombus formation during angioplasty procedures, Coller et al. can be combined with the other references to show that it would be obvious to use the chimeric molecules of the present invention in combination with a surgical procedure.

In contrast to Coller et al., Cummings et al. is directed to the treatment of acute inflammatory conditions not thrombus formation. Accordingly, there is no factual basis or motivation for combining these references as suggested by the Examiner. Moreover, claims 40, 41, 49 and 50 are directed to decreasing the formation of atherosclerotic lesions in conjunction with a surgical procedure, and these claims are even further removed from the ambit of these references.

CONCLUSION

Claims 40, 41, 49-52, 59, 60 and 73 are deemed to be patentable over the Cummings et al., Tedder et al. and Coller et al. references, and to overcome the sole remaining ground of rejection in this application. Appellants submit that a fair and objective reading of the Wagner declaration would lead to the conclusion that appellants have effectively antedated the Cummings et al. primary reference, and removed it from consideration as a basis for rejecting Claims 40, 51 and 73, and claims dependent thereon. Notwithstanding, appellants also maintain that the references fail to teach a method for preventing the growth or formation of atherosclerotic lesions in a mammal in combination with a surgical technique as recited in appended claims 40, 41, 49 and 50.

Accordingly, for the reasons presented in this brief, appellants respectfully urge the Board to reverse the rejection made in the Final Office Action, and to allow all of the appended claims.

Appellants hereby authorize the Commissioner, to debit the $330.00 fee for filing this appeal brief from Appellant's Deposit Account No. 18-1945. If there are any other fees not accounted for above, Appellants hereby authorize the Commissioner to charge the fee to Deposit Account 18-1945.

Respectfully submitted,

ROPES & GRAY

Date:

William G. Gosz
Reg. No. 27,787
Attorney for Appellants
Patent Group
Ropes & Gray
One International Place
Boston, MA 02110

APPENDIX

40. A method for decreasing the formation or growth of atherosclerotic lesions in a mammal comprising:

providing a soluble chimeric construct comprising P-selectin glycoprotein ligand-1 or a fragment thereof and another molecule, said chimeric construct being capable of inhibiting the interaction between P-selectin and a ligand of P-selectin; and

administering to a mammal an effective amount of said chimeric construct such that said P-selectin-ligand interaction is inhibited, wherein said chimeric construct is administered prior to, or in conjunction with, a vessel-corrective technique.

41. The method of claim 40, wherein said vessel-corrective technique is selected from the group consisting of angioplasty, stenting procedure, atherectomy, and bypass surgery.

49. The method of claim 40, wherein said chimeric construct is administered in sequential exposures over a period of hours, days, weeks, months or years.

50. The method of claim 40, wherein said chimeric construct is administered in combination with other therapeutic agents.

51. A method for treating or inhibiting atherosclerosis in a mammal comprising:

providing a soluble chimeric construct comprising P-selectin glycoprotein ligand-1 or a fragment thereof and another molecule, said chimeric construct being capable of inhibiting the interaction between P-selectin and a ligand of P-selectin; and

administering to a mammal an effective amount of said chimeric construct such that said P-selectin-ligand interaction is inhibited, wherein said chimeric construct is administered prior to, or in conjunction with, a vessel-corrective technique.

52. The method of claim 51, wherein said vessel-corrective technique is selected from the group consisting of angioplasty, stenting procedure, atherectomy, and bypass surgery.

59. The method of claim 51, wherein said chimeric construct is administered in sequential exposures over a period of hours, days, weeks, months or years.

60. The method of claim 51, wherein said chimeric construct is administered in combination with other therapeutic agents.

73. A method for treating restenosis in a mammal to which a vessel-corrective technique is administered comprising:

performing a vessel-corrective technique selected form the group consisting of angioplasty, stenting procedure, atherectomy, and bypass surgery on a mammal; and

administering to said mammal, after said vessel-corrective technique, an effective amount of a soluble chimeric construct comprising P-selectin glycoprotein ligand-1 or a fragment thereof, and another molecule, said chimeric construct being capable of inhibiting the interaction between P-selectin and a ligand of P-selectin, such that the restenosis occurring after said vessel-corrective technique is thereby treated.

PTO/SB/92 (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application No. (if known): 09/436076 Attorney Docket No.: CFBF-P03-002

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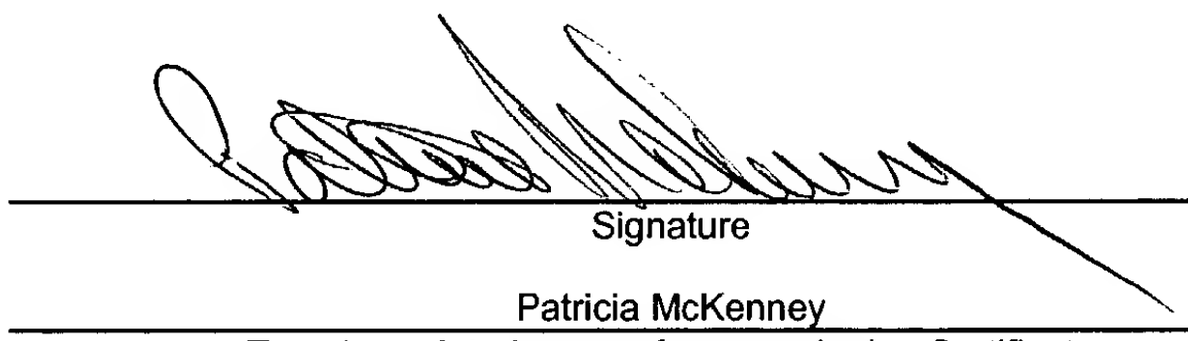

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